971700

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

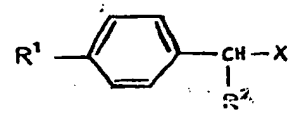
Anti-Inflammatory Agents

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to phenylalkane derivatives. More particularly it relates to novel pharmaceutical and veterinary compositions which comprise as the active ingredient one or more members of a specified group of derivatives of toluene. The invention also relates to the provision of novel members of this specified group of compounds.

It is an object of the invention to provide therapeutic compositions for the relief of pain, fever and inflammation in man and animals which do not suffer from the disadvantages of similar therapeutic compositions based on aspirin, phenylbutazone or adrenocorticosteroids.

We have now discovered that compounds of the general formula I



I

wherein R^1 represents ethyl, propyl, butyl, alkenyl (C_2—C_4), pentyl (except n-pentyl), alkoxy (C_2—C_3), allyloxy, phenoxy, phenylthio or cycloalkyl (C_5—C_7) optionally substituted by methyl or ethyl in the 1-position, R^2 represents hydrogen or methyl and X represents the radical COOH, $COOR^3$ wherein R^3 represents alkyl (C_1—C_8) or optionally *N*-alkylated aminoalkyl (C_2—C_8), COOM wherein M represents the ammonium ion or a single equivalent of a non-toxic metallic cation, COOH.B wherein B represents a non-toxic organic base, $CONH_2$, CH_2NH_2 or the group CH_2OR^4 where R^4 represents hydrogen or lower alkanoyl (C_1—C_3) have valuable anti-inflammatory, analgesic and antipyretic properties.

Furthermore in general the compounds exhibit low toxicity and low irritancy to the gastric mucosa, they do not have other undesirable pharmacological activities which might give rise to unwanted side effects and they are stable in the presence of water.

According to the present invention there are provided therapeutic compositions comprising as active ingredient one or more compounds of the general formula I in association with a pharmaceutically acceptable diluent or carrier.

The following compounds are typical of the active compounds of the general formula I, but do not limit the invention in any way:—

4-*n*-Propylphenylacetic acid
4-Ethoxyphenylacetic acid
4-Isopropylphenylacetic acid
4-propoxyphenylacetic acid
4-Isopropoxyphenylacetic acid
4-*s*-Butylphenylacetic acid
4-Allyloxyphenylacetic acid
4-*t*-Butylphenylacetic acid
4-Cyclopentylphenylacetic acid
4-*iso*butylphenylacetic acid
4-Cycloheptylphenylacetic acid
4-Cyclohexylphenylacetic acid
4-(1-Ethylpropyl)phenylacetic acid
4-Phenoxyphenylacetic acid
4-(1,2-dimethylpropyl)phenylacetic acid
4-Phenylthiophenylacetic acid
α-(4-Cyclohexylphenyl)propionic acid

[*Price 4s. 6d.*]

2-(4-isobutylphenyl)ethanol
2-(4-Cyclohexylphenyl)ethanol
4-Vinylphenylacetic acid
2-(4-Isopentylphenyl)propanol
Ammonium 4-*t*-Butylphenylacetate
4-*t*-Butylphenylacetamide
2-(4-Cyclohexylphenyl)propanol
4-(2,2-dimethylpropyl)phenylacetic acid
octyl 4-*t*-Butylphenylacetate
4-(1-Methylcyclohexyl)phenylacetic acid
Octyl α-(4-cyclohexylphenyl)propionate
4-(1-Ethylcyclohexyl)phenylacetic acid
Ethyl 4-*t*-butylphenylacetate
4-(2-Methylbutyl)phenylacetic acid
Sodium α-(4-cyclohexylphenyl)propionate
Methyl 4-*t*-butylphenylacetate
Sodium 4-*t*-butylphenylacetate
n-Propyl α-(4-isopentylphenyl)propionate
Butyl 4-*t*-butylphenylacetate
Isopropyl 4-*t*-butylphenylacetate
n-Propyl 4-*t*-butylphenylacetate
2-(4-*t*-Butylphenyl)ethanol
2-(4-*t*-Butylphenyl)ethyl propionate
2-(4-isobutylphenyl)propanol
α-(4-isobutylphenyl)propionic acid
4-*t*-Pentylphenylacetic acid
2,4¹-(1-Methylcyclohexyl)phenyl ethanol
2-(4-isopentylphenyl)ethanol
Ethyl-4-isobutylphenylacetate
Benzylamine 4-*t*-butylphenylacetate
α-(4-*t*-Butylphenyl)propionic acid
α-(4-isopentylphenyl)propionic acid
2-4¹-*t*-Butylphenylethylamine
Ethyl α-(4-isobutylphenyl)propionate
n-Propyl 4-isopentylphenylacetate
α-(4-*s*-Butylphenyl)propionic acid
α-4¹-(1-Ethylpropyl)phenylpropionic acid
α-4¹-(2-Methylbutyl)phenylpropionic acid
α-4¹-(2,2-dimethylpropyl)phenylpropionic acid
α-4¹-(1-Ethylcyclohexyl)phenylpropionic acid
α-(4-Ethylphenyl)propionic acid.

We have discovered that the compounds which are the active components of the compositions of the present invention are superior to acetylsalicyclic acid in that they exhibit one or more of the following advantages:—

(a) They are less toxic;
(b) They have a higher therapeutic ratio;
(c) They are more stable in the presence of water or water vapour;
(d) They are more soluble in water.

The alkali metal and alkaline earth metal salts of the acids are particularly soluble in water and they are valuable for the preparation of oral compositions.

The active compounds of the present invention may be prepared by methods which are well known for the preparation of phenylacetic acids, phenylpropionic acids and derivatives thereof. Where these processes produce novel compounds, such novel compounds are also part of the present invention.

In general the acids, salts and alcohols are relatively the most active compounds followed by the esters.

The invention comprises as new compounds of the general formula I:—

(a) the acids, and their inorganic and organic salts, in which X is COOH, R^1 is isobutyl, s-butyl, pentyl (other than n-pentyl), 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is a hydrogen or methyl, and if R^2 is methyl R^1 may also be ethyl, n-propyl, t-butyl or cyclohexyl;

(b) the alcohols in which X is CH_2OH, R^1 is isobutyl, s-butyl, pentyl (other than n-pentyl or t-pentyl), 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is hydrogen or methyl, and if R^2 is methyl R^1 may also be n-propyl, isopropyl, t-butyl or t-pentyl;

(c) the esters in which X is $COOR^3$, R^1 is isobutyl, pentyl (other than n-pentyl or t-pentyl), cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, R^2 is hydrogen or methyl, and R^3 is alkyl (C_1—C_8) or optionally N-alkylated aminoalkyl (C_2—C_8), and if R^3 is other than ethyl or if R^2 is methyl, R^1 may also be s-butyl, t-butyl or t-pentyl;

(d) the amines in which X is CH_2NH_2, R^1 is isobutyl, s-butyl, t-butyl, pentyl (other than n-pentyl), cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is hydrogen or methyl.

A list of methods suitable for preparing these compounds is given below. In these representations R^1 and R^2 are as hereinbefore defined for general formula I and Ph represents phenyl or phenylene.

Acids

1. $R^1Ph \xrightarrow[ZnCl_2]{HCl/H.CHO} R^1Ph.CH_2.Cl \rightarrow R^1Ph.CH_2.Mg.Cl.$

$\xrightarrow{CO_2} R^1Ph.CH_2COOH$

2. $R^1Ph \xrightarrow[ZnCl_2]{HCl/H.CHO} R^1Ph.CH_2.Cl \rightarrow R^1Ph.CH_2CN$

$\xrightarrow{\text{hydrolyse}} R^1Ph.CH_2COOH$

3. $R^1Ph \xrightarrow[ZnCl_2]{HCl/H.CHO} R^1.Ph.CH_2.Cl \rightarrow R^1Ph.CH_2CN$

$\xrightarrow{NaNH_2} R^1Ph.\underset{\displaystyle Na}{\underset{|}{CH}}.CN. \xrightarrow{MeI} R^1Ph.\underset{\displaystyle CH_3}{\underset{|}{CH}}.CN$

$\xrightarrow{\text{hydrolyse}} R^1Ph.\underset{\displaystyle CH_3}{\underset{|}{CH}}.COOH$

4. $R^1Ph \xrightarrow[AlCl_3]{CH_3COCl} R^1Ph.CO.CH_3 \xrightarrow[\text{and hydrolyse}]{\text{Willgerodt}} R^1Ph.CH_2.COOH$

5. $R^1Ph.CH_2.COOEt \xrightarrow[NaOEt]{(EtO)_2CO} R^1Ph.CH(COOEt)_2$

$\xrightarrow[NaOET]{MeI} R^1Ph.CMe(COOEt)_2 \xrightarrow{\text{hydrolyse}} R^1Ph.CMe(COOH)_2$

$\xrightarrow{\text{decarboxylate}} R^1Ph.\underset{\displaystyle CH_3}{\underset{|}{CH}}.COOH$

6. $R^1Ph.\underset{\displaystyle R^3}{\underset{|}{CH}}.COOR^3 \xrightarrow{\text{hydrolyse}} R^1Ph.\underset{\displaystyle R^3}{\underset{|}{CH}}.COOH$

(R^3 is alkyl, aryl or aralkyl)

Acids

7. $R^1Ph \xrightarrow{COCl.COOR^3} R^1Ph.CO.COOR^3 \xrightarrow{MeMgBr}$

$R^1Ph.\underset{\underset{CH_3}{|}}{C}(OH).COOR^3 \xrightarrow{\text{hydrolyse}} R^1Ph.\underset{\underset{CH_3}{|}}{C}.(OH).COOH \xrightarrow{P/I} R^1Ph.\underset{\underset{CH_3}{|}}{CH}.COOH$

(R^3 is alkyl)

8. $R^1Ph.Br \rightarrow R^1Ph.MgBr \xrightarrow{CH_3.CO.COOEt} R^1Ph.\underset{\underset{CH_3}{|}}{C}(OH).COOEt \xrightarrow{\text{hydrolyse}} R^1Ph.\underset{\underset{CH_3}{|}}{C}(OH).COOH \xrightarrow{P/I} R^1Ph.\underset{\underset{CH_3}{|}}{CH}.COOH$

9. $R^1Ph.COCH_3 + HCN \rightarrow R^1Ph.\underset{\underset{CN}{|}}{C}(OH).CH_3 \xrightarrow{HI/P} R^1Ph.\underset{\underset{CH_3}{|}}{CH}.COOH$

10. $R^1Ph + CH_3.\underset{\underset{O.SO_2C_6H_5}{|}}{CH}.CN \xrightarrow{AlCl_3} R^1Ph.\underset{\underset{CH_3}{|}}{CH}.CN \xrightarrow{\text{hydrolyse}} R^1Ph.\underset{\underset{CH_3}{|}}{CH}.COOH$

11. Alcohols and aldehydes may be oxidised to the corresponding acids.

Esters

1. $R^1Ph.\underset{\underset{R^2}{|}}{CH}.COOH + R^3OH \xrightarrow{H_2SO_4} R^1Ph.\underset{\underset{R^2}{|}}{CH}.COOR^3$

2. $R^1Ph.\underset{\underset{R^2}{|}}{CH}.COOH \rightarrow R^1Ph.\underset{\underset{R^2}{|}}{CH}.COCl \xrightarrow{R^3OH} R^1Ph.\underset{\underset{R^2}{|}}{CH}.COOR^3$

Esters

3. $R^1Ph. \rightarrow R^1Ph.Cl. \rightarrow R^1Ph.Mg.Cl \xrightarrow{Br.CH(R^2).COOR^3}$

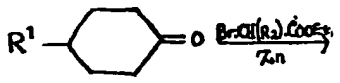
$$R^1Ph.\underset{\displaystyle R^2}{\underset{|}{CH}}.COOR^3$$

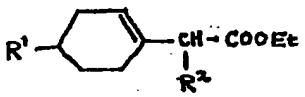
4. $R^1Ph \xrightarrow{COCl.COOR^3} R^1Ph.CO.COOR^3 \xrightarrow{H} R^1Ph.CH_2.COOR^3$

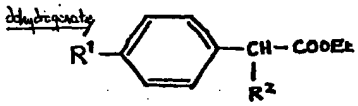
5. $R^1Ph.CH_2.COOR^3 \xrightarrow{NaH} R^1Ph.CHNa.COOR^3 \xrightarrow{MeI}$

$$R^1Ph.\underset{\displaystyle CH_3}{\underset{|}{CH}}.COOR^3$$

6.







7. $R^1Ph.\underset{\displaystyle R^2}{\underset{|}{CH}}.COOH$ + dialkylaminoalkyl halide

$\longrightarrow$ dialkylaminoalkyl ester hydrochloride.

(R^3 is alkyl or where possible substituted alkyl e.g. diethylaminoethyl).

Alcohols

1. $R^1Ph \xrightarrow{Cl} R^1PhCl \rightarrow R^1Ph.Mg.Cl$

$$\xrightarrow{\text{Ethylene oxide}} R^1Ph.CH_2CH_2OH$$

2. $R^1Ph.\underset{\displaystyle R^2}{\underset{|}{CH}}.COOR^3 \xrightarrow{\text{hydrogenation}} R^1Ph.\underset{\displaystyle R^2}{\underset{|}{CH}}.CH_2OH$

(R^3 is H or alkyl)

The hydrogenation takes place in the presence of catalysts e.g. copper/chromium oxide, or the ester is reduced with sodium or with Li, Al, H_4 to the alcohol (Bouveault-Blanc reaction).

The salts of the acids can be made by reacting the acids with organic or inorganic bases.

The pharmaceutically acceptable diluents or carriers which are admixed with the active compound to form the compositions of this invention are well-known and the actual excipients which are used depend *inter alia* on the method of administering the compositions. The compositions of this invention may be adapted for oral, topical or parenteral use but the preferred method of administration is *per os*. In this case the oral compositions may take the form of capsules, tablets, lozenges or effervescent granules, or liquid preparations such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the aforementioned general formula; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of such compositions include those solid and liquid diluents which are compatible with the active ingredients together with colouring matter and flavouring if desired. We have found that a tablet containing the active ingredient in the form of a salt in association with maize starch as a diluent is a particularly valuable and convenient composition. Such tablets disintegrate rapidly in the stomach and generally do not set up gastric irritation. Such tablets may conveniently contain from 25 to 500 mg of the active compound.

The compositions of the invention in the form of effervescent granules may comprise a compound of the above general formula in association with a combination of effervescing agents well-known in the art. Such an effervescent combination may include for example sodium bicarbonate in association with a free acid or acid salt such as tartaric acid or sodium acid tartrate.

The liquid compositions of the invention adapted for oral use may be in the form of solutions or suspensions. Such compositions in the form of solutions may be aqueous solutions of a soluble compound of the above general formula in association with, for example, sucrose to provide a syrup. The composition in the form of suspensions may comprise an insoluble compound of the present invention in association with water together with a suspending agent, flavouring agents, colouring matter, etc.

The compositions of the invention which are adapted for topical use include ointments, creams and lotions containing compounds of the above general formula or their derivatives. Suitable ointments and creams may be water miscible or water immiscible in character and include emulsions prepared from emulsifying waxes and oils and also those prepared from water miscible polyethylene glycols. The lotions according to the invention may comprise a solution of the active ingredients of the above general formula in a suitable liquid solvent diluent which is preferably a lower aliphatic alcohol which may contain a small proportion of water.

The active ingredient of the present invention may also be incorporated into the novel compositions with other known therapeutically active compounds.

The screening test which was used to detect anti-inflammatory activity was that described by Adams and Cobb, Nature, *181*, 773, 1958.

Analgesic and antipyretic properties of the compounds were also assessed as were their toxicities on several types of animals, namely mice, rats, guinea pigs, cats and dogs. As is to be expected, the relative activities varied widely and for confirmation of the pharmacological activity in a clinical trial a compound having good all-round activity with low toxicity was chosen, namely 4-isobutylphenylacetic acid. The acute LD_{50} for this compound with mice was 1300 mg./kg. orally and 600 mg./kg. i.p.; for rats the oral figure was greater than 1200 mg./kg. No toxic effects and no pathological changes were detected in rats fed daily on 200 mg./kg. of 4-isobutylphenylacetic acid for eight weeks. Similarly no toxic effects were noted in dogs fed on 50 mg./kg. daily for six weeks.

The initial clinical trial was carried out in a controlled fashion using "double-blind" technique in which neither the patient nor the medical observer is aware of the drug being given during period of assessment. Twelve patients with acute rheumatoid arthritis involving multiple joints and with systemic febrile reaction were observed for a period of several weeks and complete symptomatic control was obtained with the oral administration of 30 grains daily of 4-isobutylphenylacetic acid in four divided doses. No toxic reactions were noted. The beneficial therapeutic effect of this treatment was indistinguishable from that obtained in the same patients with aspirin at a dose of 60 grains per day.

The evidence is that like aspirin the compounds of the present invention are useful in the treatment of (a) painful inflammation of the joints and periarticular tissues as occurs in rheumatoid arthritis, Still's disease and osteoarthritis; (b) various types of non-specific inflammatory or rheumatic conditions affecting the fibromuscular tissues and connective tissue; (c) rheumatic fever and its sequelae.

The following non-limitative examples illustrate the invention and the preparation of compounds of general formula I:—

EXAMPLE 1

4-Isobutylacetophenone (49.4 g.), sulphur (13.6 g.) and morpholine (38 ml. were refluxed for 16 hours; concentrated hydrochloric acid (344 ml.) and glacial acetic acid (206 ml.) were added and the mixture was refluxed for a further 7 hours. The mixture was cooled, diluted with water and the oil which separated was isolated with ether. The ethereal solution was extracted into aqueous sodium carbonate from which the crude acid was precipitated by addition of hydrochloric acid. The crude acid was again isolated with ether, the solution washed with water and evaporated to dryness to give a crystalline residue. The residue was crystallised from light petroleum (b.p. 40—60° C.) to give 4-isobutyl-phenylacetic acid m.p. 85.5—87.5° Found, C, 751; H, 8.5. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.3%

The following compounds were made by the same method:

4-Cycloheptylphenylacetic acid m.p. 90.5—92.5° C.

(Found: C, 77.3; H, 8.7. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%)

4-(1-Ethylpropyl)phenylacetic acid b.p. 153—154°C./2.5 mm.

(Found: C, 75.4; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

4-(1,2-Dimethylpropyl)phenylacetic acid b.p. 156—7°C./2.5 mm.

(Found: C, 75.5; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

4-(2,2-Dimethylpropyl)phenylacetic acid m.p. 110.5—111° C.

(Found: C, 75.6; H, 8.5. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

4-(2-Methylbutyl)phenylacetic acid m.p. 38—40° C.

(Found: C, 75.5; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

4-(1-Methylcyclohexyl)phenylacetic acid b.p. 194—6°C./3 mm.

(Found: C, 77.8; H, 8.4. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%)

4-(1-Ethylcyclohexyl)phenylacetic acid, b.p. 188°/0.7 mm.

(Found: C, 77.5; H, 8.2. $C_{16}H_{22}O_2$ requires C, 78.0; H, 8.9%)

4-Isopentylphenylacetic acid, m.p. 62.5—63.5° C.

(Found: C, 76.1; H, 8.6. $C_{13}H_{18}9_2$ requires C, 75.8; H, 8.7%)

4-(1-Methylbutyl)phenylacetic acid, b.p. 114°/1.5 mm.

(Found: C, 75.4; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

EXAMPLE 2

4-*s*-Butylacetophenone (40 g.) sulphur (11 g.) and morpholine (30 ml.) were refluxed for 16 hours, cooled, acetic acid (170 ml.) and concentrated hydrochloric acid (280 ml.) were added and the mixture was refluxed for a further 7 hours. The mixture was concentrated *in vacuo* to remove acetic acid and the concentrate was diluted with water. The oil which separated was isolated with ether, the ethereal solution was extracted with aqueous sodium carbonate and this extract was acidified with hydrochloric acid. The oil was isolated with ether, evaporated to dryness and the residue was esterified by refluxing with ethanol (100 ml.) and concentrated sulphuric acid (3 ml.) for 5 hours. The excess alcohol was distilled off, the residue was diluted with water and the oil which separated was isolated with ether. The ethereal solution was washed with sodium carbonate solution; then with water and was dried. The ether was evaporated off and the oil was distilled to give ethyl 4-*s*-butylphenylacetate b.p. 114—116° C/1.5 mm. (Found: C, 76.4; H, 9.0. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.1%).

Ethyl 4-*s*-butylphenylacetate (7.8 g.) was refluxed for 1 hour with sodium hydroxide solution (5N. 10 ml.) and methanol (10 ml.), acidified with hydrochloric acid and the oil which separated was isolated with ether. The ethereal solution was washed with water, dried and distilled to give 4-*s*-butylphenyl-

acetic acid b.p. 134° C/0.5 mm. (Found: C, 74.9; H, 8.5. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.3%).

In a similar manner the following compound was prepared from the appropriate ester.

4-*t*-Pentylphenylacetic acid b.p. 156° C/2.5 mm. (Found: C, 75.6; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%).

EXAMPLE 3

4-*t*-Butylphenylacetic chloride (10.5 g.) was added dropwise to *n*-butanol (12 ml.) and the mixture was heated on the steam bath for 30 minutes. The product was distilled to give as a colourless oil butyl 4-*t*-butylphenylacetate b.p. 126° C/1 mm. (Found: C, 77.7; H, 9.6. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%).

Similarly there was prepared:—

Octyl 4-*t*-butylphenylacetate b.p. 162°C/1 mm.

(Found: C, 78.9; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.5%)

Methyl 4-*t*-butylphenylacetate b.p. 106°C/ 2.5 mm.

(Found: C, 76.1; H, 8.8. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%)

Isopropyl 4-*t*-butylphenylacetate b.p. 114°C/ 1.5 mm.

(Found: C, 76.6; H, 9.2. $C_{15}H_{22}O_2$ requires C, 77.0; H, 9.4%).

n-Propyl 4-t-butylphenylacetate b.p. 112°C/ 1 mm.

(Found: C, 76.9; H, 9.5. $C_{15}H_{22}O_2$ requires C, 77.0, H, 9.4%).

EXAMPLE 4

4-*t*-Butylphenylacetamide (12.3 g.) was placed in a Soxhlet extractor and extracted with boiling ether into a solution of lithium aluminium hydride (3.0 g.) in dry ether (500 ml.). After refluxing for 6 hours the mixture was decomposed with water and the ethereal filtrate from aluminium hydroxide was extracted with very dilute hydrochloric acid. The aqueous solution was basified with sodium hydroxide solution (5N) and the oil isolated in ether and distilled to give 2-4[1]-*t*-butylphenylethylamine b.p. 92° C/2 mm. as a colourless oil. (Found: C, 81.0; H, 11.0; N, 7.6. $C_{12}H_{19}N$ requires C, 81.3; H, 10.7; N, 7.9%).

EXAMPLE 5

Sodium ethoxide from sodium (3.67 g.) in absolute alcohol (64 ml.) was added over 20 minutes with stirring to a mixture of ethyl 4-*t*-butylphenylacetate (28.14 g.) and ethyl carbonate (102 ml.) at 100° C. The reaction flask was fitted with a Fenske column through which alcohol and then ethyl carbonate distilled. After 1 hour when the still head reached 124°C heating was discontinued. Glacial acetic acid (12 ml.) and water (50 ml.) was added to the stirred ice cooled mixture and the ester isolated in ether, washed with sodium carbonate solution, water and distilled to give ethyl 4-*t*-butylphenylmalonate b.p. 144° C/1.5 mm. (Found: C, 70.4; H, 8.4. $C_{17}H_{24}O_4$ requires C, 69.9; H, 8.2%).

Ethyl 4-*t*-butylphenylmalonate (27.53 g.) in absolute alcohol (25 ml.) was added with sodium (2.17 g.) in absolute alcohol (75 ml.). Methyl iodide (15 ml.) was added and the mixture refluxed for 2½ hours, the alcohol distilled and the residue diluted with water, extracted with ether, washed with sodium bisulphite, water, and evaporated to dryness.

The residual oil was stirred and refluxed with sodium hydroxide (75 ml. of 5*N*) water (45 ml.) and industrial alcohol (120 ml.). Within a few minutes a sodium salt separated and after 1 hour the solid was collected, washed with ethanol, dissolved in hot water and acidified with dilute hydrochloric acid to give the *C*-methyl malonic acid which was collected and dried *in vacuo* m.p. 177—180° (dec.).

The malonic acid (9 g.) was heated to 210—220°C. in an oil bath for 20 minutes until decarboxylation had ceased. The propionic acid was cooled and recrystallised from light petroleum (b.p. 60—80°C).

Two further recrystallisations from the same solvent gave colourless prisms of 2-4[1]-*t*-butylphenylpropionic acid m.p. 101—103.5° C. (Found: C, 75.4; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%).

In the same manner the following were prepared:—

2-4[1]-Cyclohexylphenylpropionic acid m.p. 110.5—112.5°C.

(Found: C, 77.8; H, 8.1. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%).

2-4[1]-Isobutylphenylpropionic acid m.p. 75—77.5°C.

(F und: C, 75.3; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.8; H, 8.7%).

EXAMPLE 6

Propionyl chloride (4.9 g.) was added to a mixture of 2-4'-*t*-butylphenylethanol (6 g.) and dry pyridine (6 ml.) and the mixture was heated under anhydrous conditions for 30 minutes on the steam bath. The reaction mixture was poured into water, acidified with 5*N* sulphuric acid and the oily product was collected with ether. The ether was distilled to give 2-4'-*t*-butylphenylethyl propionate as an oil b.p. 131—2°C/1.5 mm. (Found: C, 77.0; H, 9.1. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.4%).

EXAMPLE 7

4-Isobutylcyclohexanone (34.28 g.) zinc filings (analytical grade) (16.0 g.) ethyl bromoacetate (26.5 ml.) and dry benzene (120 ml.) were warmed until a vigorous reaction set in which required external cooling. The mixture was then refluxed for 30 minutes, decomposed with ice cold dilute sulphuric acid, the benzene solution separated, washed with water, dried and evaporated. The residue (49 g.) dry pyridine (45 ml.) dry ether (93 ml.) were stirred with ice cooling and thionyl chloride (26 ml.) added dropwise over 30 minutes, the temperature being held below 12°C. After stirring for 2 hours at 0°C, water was cautiously added to the reaction mixture, the ethereal solution was washed with water, dried and ethyl 4-isobutylcyclohex-1-enylacetate was distilled; b.p. 106—109° C/2 mm. (Found: C, 75.0; H, 10.4. $C_{14}H_{24}O_2$ requires C, 75.0; H, 10.7%).

Ethyl 4-isobutylcyclohex-1-enylacetate 8.0 g.) and sulphur (2.7 g.) were heated at 210° for 5 hours, then at 240°C for 2 hours. Copper powder (100 mg.) was added and the heating continued for 5 minutes; the mixture was cooled, diluted with ether, filtered and ethyl 4-isobutylphenylacetate was distilled; b.p. 110° C/1 mm. (Found: C, 76.7; H, 9.2. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.1%).

EXAMPLE 8

4-Isobutylbenzyl chloride (50 g.), sodium cyanide (16.1 g.), alcohol (100 ml.), water (30 ml.) were refluxed and stirred for 5 hours. The alcohol was distilled, the oil isolated in ether, washed with water and distilled. b.p. 113°C/2 mm.

4-Isobutylphenylacetonitrile (30 g.), alcohol (100 ml.), 5*N* sodium hydroxide (60 ml.) were refluxed for 6 hours and the alcohol removed by distillation. The residue was acidified with dilute hydrochloric acid and the precipitate collected in ether, extracted with dilute sodium carbonate solution, and the extracts acidified with dilute hydrochloric acid. The crystalline precipitate of 4-isobutylphenylacetic acid was collected, washed with water dried *in vacuo* and recrystallised from light petroleum.

EXAMPLE 9

To an ice cold stirred solution of anhydrous aluminium chloride (40.0 g.) in nitrobenzene (125 ml.) was slowly added ethyl oxalyl chloride (27.4 g.) followed by the dropwise addition of isobutyl benzene (36.1 g). After stirring for 5 hours at room temperature the mixture was decomposed with cracked ice, ether (200 ml.) added and the organic phase washed with sodium hydrogen carbonate solution, water and distilled; b.p. 155° C/3 mm.

Ethyl 4-isobutylphenylglyoxylate (11.0 g.) was hydrogenated at room temperature and 2 atmospheres of hydrogen in the presence of palladium black (1.0 g.) and glacial acetic acid (80 ml.). When absorption of hydrogen had ceased, perchloric acid (7 g. of 70%) was added and hydrogenation continued until absorption was complete. The filtrate from the catalyst was treated with aqueous sodium hydroxide to neutralise the perchloric acid and acetic acid was distilled *in vacuo* below 50°C. The residue was hydrolysed by refluxing and stirring with 2*N* sodium hydroxide (50 ml.) for 6 hours, cooled and acidified with dilute hydrochloric acid, the precipitate of 4-isobutylphenylacetic acid collected, washed with water, dried *in vacuo* and recrystallised from light petroleum; (b.p. 62—68°C).

EXAMPLE 10

Benzylamine 4-*t*-butylphenylacetate

4-*t*-Butylphenylacetic acid (1.35 g.) and benzylamine (0.75 g.) were mixed in ether (30 ml.) and the salt collected and recrystallised from absolute alcohol in colourless plates; m.p. 144—147°C. (Found: N, 4.8. $C_{19}H_{25}NO_2$ requires N, 4.7%).

EXAMPLE 11

Diethylaminoethyl 4-*t*-butylphenylacetate

N,N-Diethylaminoethanol (10.0 g.) in dry ether (50 c.c.) was added dropwise to a stirred solution of 4 - *t* - butylphenylacetyl chloride (15.0 g.) in dry ether (100 cc.) at 0—5°C. After stirring for 1 hour at room temperature, water (20 cc.) was added and the ether extracted twice with 2*N* hydrochloric acid. The aqueous solutions were combined, basified with 2*N* sodium hydroxide and the oil isolated in ether washed with water, dried and distilled b.p. 156—160°C/1.5 mm. 8.5 g., 34%. Re-distilled to give a practically colourless liquid b.p. 153—154°C/1.5 mm. (Found: N, 5.2. $C_{18}H_{29}NO_2$ requires N, 4.8%).

EXAMPLE 12

2,4'-Isobutylphenylethanol

Ethyl 4-isobutylphenylacetate (15 g.) in dry ether (50 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (3 g.) in ether (150 ml.). The mixture was refluxed for 1 hour, decomposed with dilute sulphuric

acid; the ether layer was separated and washed with water, dried and distilled to give 2-4¹-isobutylphenylethanol; b.p. 104°C/0.8 mm. (Found: C, 80.3; H, 10.0; $C_{12}H_{18}O$ requires C, 80.9; H, 10.1%).

EXAMPLE 13

Ethyl 4-isobutylphenylacetate

4-Isobutylphenylacetic acid (75 g.), absolute alcohol (500 ml.) and concentrated sulphuric acid (15 ml.) were refluxed for 4 hours. Excess alcohol was distilled *in vacuo*, the residue diluted with water and the ester was isolated in ether, washed with sodium carbonate solution, then water before being dried and distilled; its b.p. was 108—110°C/0.6 mm. (Found: C, 76.7; H, 9.2. $C_{14}H_{20}O_2$ requires C, 76.4; H, 9.1%).

In the same manner the following compounds were made:—

Ethyl 4 - cyclohexylphenylacetate; b.p. 140°C/1 mm. (Found: C, 78.5; H, 9.2. $C_{16}H_{22}O_2$ require C, 78.0; H, 8.9%).

Ethyl 2 - 4¹ - isobutylphenylpropionate; b.p. 107°C/1 mm. (Found: C, 76.8; H, 9.6. $C_{15}H_{22}O_2$ requires C, 77.0; H, 9.4%).

EXAMPLE 14

An intimate mixture was prepared of equal parts of 4-isobutylphenylacetic acid and a tablet base comprising starch with the addition of 1% magnesium stearate as a lubricant. The mixture was compressed into tablets containing 2½ grains of 4-isobubtylphenylacetic acid.

Similar tablets were also prepared but using as the active ingredient the sodium salt of this acid, and also other compounds of the present invention such as 4-isobutylphenylpropionic acid or 4-cyclohexylphenylacetic acid.

EXAMPLE 15

An intimate mixture was made of 5 parts of 4-isobutylphenylacetic acid and 3 parts of a tablet base comprising starch with the addition of 1% magnesium stearate as a lubricant. The mixture was compressed into tablets containing 5 grains of 4-isobutylphenylacetic acid.

Similar tablets were also prepared but using as the active ingredient the sodium salt of this acid, and also other compounds of the invention such as 4-isobutylphenylpropionic acid or 4-cyclohexylphenylacetic acid.

EXAMPLE 16

A mixture was prepared from the following ingredients:

Sodium 4-isobutylphenylacetate		13.7 g.
Concentrated orange peel infusion		62.5 ml.
Chloroform water	to	1,000 ml.

A dose of the above mixture is contained in 15 ml.

EXAMPLE 17

A suspension was prepared from the following ingredients:

4-Isobutylphenylacetic acid		13.7 g.
Compound tragacanth powder		22.9 g.
Chloroform water	to	1,000 ml.

A dose of the above suspension is contained in 15 ml.

EXAMPLE 18

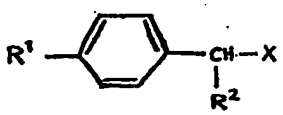
An elixir was prepared from the following ingredients:

Sodium 4-cyclohexylphenyl acetate		13.7 g.
Ethanol (90%)		400 ml.
Glycerol		333 ml.
Compound orange spirit		33 ml.
Compound tartrazine solution		10.4 ml.
Water	to	1,000 ml.

Dose—15 ml.

WHAT WE CLAIM IS:—

1. Therapeutic compositions comprising a compound of the general formula I:—



..... I

wherein R^1=ethyl, propyl, butyl, alkenyl (C_2—C_4), pentyl (except n-pentyl), alkoxy (C_2—C_3), allyloxy, phenoxy, phenylthio, cycloalkyl (C_5—C_7) optionally substituted by methyl or ethyl in 1-position; R^2=H or CH_3; X=COOH; $COOR^3$ wherein R^3=alkyl (C_1—C_8) or optionally *N*-alkylated aminoalkyl (C_2—C_5); COOM wherein M=NH_4 or a single equivalent of a non-toxic metallic cation; COOH.B wherein B=a non-toxic organic base; $CONH_2$; CH_2NH_2; CH_2OR^4 wherein R^4=H or alkanoyl (C_1 to C_3) in association with a solid or liquid pharmaceutically acceptable diluent or carrier.

2. Solid compositions as claimed in claim 1 in the form of capsules, tablets, lozenges and effervescent granules.

3. Liquid compositions as claimed in claim 1 in the form of mixtures, elixirs, syrups and suspensions.

4. Compositions as claimed in claim 1 in the form of ointments, creams and lotions.

5. A solid composition as claimed in claim 2 comprising 4-isobutylphenylacetic acid or a non-toxic salt thereof.

6. A tablet capsule or lozenge as claimed in claim 2 comprising 25—500 mg. of a compound falling within the general formula I.

7. A composition as claimed in claim 6 in which the compound is 4-isobutylphenylacetic acid or a non-toxic salt thereof.

8. A composition as claimed in claim 6 in which the compound is sodium 4-isobutylphenylacetate.

9. A composition as claimed in claims 5—8,

wherein the pharmaceutical base of the composition comprises starch and magnesium stearate.

10. A composition as claimed in claim 9 in the form of a tablet comprising 2½—5 grains of 4-isobutylphenylacetic acid or sodium salt thereof.

11. Acids, and their inorganic and organic salts, of the general formula I in which X is COOH, R^1 is isobutyl, s-butyl, pentyl (other than n-pentyl), 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is a hydrogen or methyl, and if R^3 is methyl R^1 may also be ethyl, n-propyl, t-butyl or cyclohexyl.

12. Alcohols of the general formula I in which X is CH_2OH, R^1 is isobutyl, s-butyl, pentyl (other than n-pentyl or t-pentyl), 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is hydrogen or methyl, and if R^2 is methyl R^1 may also be n-propyl, isopropyl, t-butyl or t-pentyl.

13. Esters of the general formula I in which X is $COOR^3$, R^1 is isobutyl, pentyl (other than n-pentyl or t-pentyl), cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, R^2 is hydrogen or methyl, and R^3 is alkyl (C_1—C_8) or optionally N-alkylated aminoalkyl (C_2—C_8), and if R^2 is other than ethyl or if R^2 is methyl, R^1 may also be s-butyl, t-butyl or t-pentyl.

14. Amines of the general formula I in which X is CH_2NH_2, R^1 is isobutyl, s-butyl, t-butyl, pentyl (other than n-pentyl), cyclohexyl, 1-methylcyclohexyl, 1-ethylcyclohexyl or cycloheptyl, and R^2 is hydrogen or methyl.

15. 4-Isobutylphenylacetic acid.
16. 4-*s*-butylphenylacetic acid.
17. 4-(1-ethylpropyl)phenylacetic acid.
18. 4-(1,2-dimethylpropyl)phenylacetic acid.
19. 4-(2,2-dimethylpropyl)phenylacetic acid.
20. 4-(2-methylbutyl)phenylacetic acid.
21. 4-cycloheptylphenylacetic acid.
22. 4-(1-methylcyclohexyl)phenylacetic acid.
23. Butyl 4-*t*-butylphenylacetate.
24. Methyl 4-*t*-butylphenylacetate.
25. Isopropyl 4-*t*-butylphenylacetate.
26. n-Propyl 4-*t*-butylphenylacetate.
27. Octyl 4-t-butylphenylacetate.
28. *alpha*-(4-*t*-butylphenyl)propionic acid.
29. 4-(1-ethylcyclohexyl)phenylacetic acid.
30. Sodium 4-isobutylphenylacetate.
31. Ethyl 4-isobutylphenylacetate.
32. Ethyl 4-cyclohexylphenylacetate.
33. 2-(4-isobutylphenyl)ethanol.
34. *alpha*-(4-isobutylphenyl)propionic acid.
35. *alpha* - (4 - cyclohexylphenyl)propionic acid.
36. Ethyl *alpha* - (4 - isobutylphenyl)propionate.
37. Novel compounds and compositions as described in the specification and claimed in any preceding claim, with particular reference to the Examples.

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